REMARKS

Claims 1-7, and 11-15 are pending in this application. Claims 8-10 and 16- 23 have been previously canceled without prejudice or disclaimer.

Claims 1, 4, 6, 11, 14 and 15 have been amended for the sole reason of advancing prosecution. Applicants, by canceling or amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claim 1 has been amended to recite a "method for treating a respiratory disease in a patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; and a pharmaceutically acceptable carrier." Support for claim 1, as amended, can be found throughout the specification and claims as originally filed, for example, second paragraph, page 8 of the present specification. Claims 2, 3 and 5 depend from claim 1.

Claim 4 has been amended to recite a "method for treating muscular dysfunction in a COPD patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin,

Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; and a pharmaceutically acceptable carrier." Support for claim 4, as amended, can be found throughout the specification and claims as originally filed, for example, second paragraph, page 8 of the present specification.

Claim 6 has been amended to recite a "method for treating COPD in a patient consisting of the step of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; and a pharmaceutically acceptable carrier." Support for claim 6, as amended, can be found throughout the specification and claims as originally filed, for example, second paragraph, page 8 of the present specification. Claim 7 depends from claim 6.

Claim 11 has been amended to recite a "method for treating a respiratory disease in a patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds in combination with a therapeutically effective amount of a further compound selected from

the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate; and a pharmaceutically acceptable carrier. Support for claim 11, as amended, can be found throughout the specification and claims as originally filed, for example, second paragraph, page 8 of the present specification. Claims 12 and 13 depend from claim 11.

Claim 14 has been amended to recite a "method for treating muscular dysfunction in a COPD patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds, in combination with a therapeutically effective amount of a further compound selected from the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate, and a pharmaceutically acceptable carrier." Support for claim 14, as amended, can be found throughout the specification and claims as originally filed, for example, second paragraph, page 8 of the present specification.

Claim 15 has been amended to recite a "method for treating COPD in a patient consisting of the step of administering a therapeutically effective amount of a compound

selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds in combination with a therapeutically effective amount of a further compound selected from the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate; and a pharmaceutically acceptable carrier." Support for claim 15, as amended, can be found throughout the specification and claims as originally filed, for example, second paragraph, page 8 of the present specification.

No new matter has been added.

In view of the remarks set forth herein, further and favorable consideration is respectfully requested.

I. At page 3, of the Official Action, claims 1-7 and 11-15 have been rejected under 35 USC § 112, first paragraph.

The Examiner asserts that the specification does not provide sufficient support for the transitional phrase "consisting essentially of."

In view of the following, this rejection is respectfully traversed.

Claims 1, 4, 6, 11, 14 and 15 have been amended to recite the transitional phrase "consisting of," instead of "consisting essentially of." As indicated in MPEP § 2111.03, the

phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. Accordingly, the use of the phrase "consisting of" does not place any additional burden on the Applicants to show that the introduction of additional components would materially change the characteristics of the presently claimed subject matter.

Applicants submit that amended claims 1, 4, 6, 11, 14 and 15 now comply with the written description requirement of 35 USC § 112, first paragraph. Thus, the Examiner is respectfully requested to reconsider and withdraw this rejection.

II. At pages 3-4, of the Official Action, claims 1-4 and 6 have been rejected under 35 USC § 103(a) as unpatentable over Manning (US 2004/0087653) in view of Schmid et al. (WO 2001/56551).

The Examiner asserts that it would have been obvious to combine the methods for the treatment of respiratory diseases and conditions using a selective iNOS inhibitor and a PDE inhibitor as described in Manning with the use of BH4 as described in Schmid et al. to arrive at the presently claimed subject matter.

In view of the following, Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to

determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *See KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 at 417-418. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because, whether taken alone or in combination, neither Manning nor Schmid et al. teach or suggest each and every element of the presently pending claims as required by *In re Wilson.*

As amended, claim 1 is directed to a method for treating a respiratory disease in a patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-

5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; and a pharmaceutically acceptable carrier. Claims 2 and 3 depend from claim 1.

Claim 4 is directed to a method for treating muscular dysfunction in a COPD patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; and a pharmaceutically acceptable carrier.

Claim 6 is directed to a method for treating COPD in a patient consisting of the step of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; and a pharmaceutically acceptable carrier.

In contrast to the presently claimed subject matter, Manning describes methods for the treatment of respiratory diseases comprising administering a selective inhibitor of inducible nitric oxide synthase and a PDE inhibitor. *See* Manning at the Abstract.

However, Manning does not teach or suggest every element of the presently claimed subject matter. Nowhere does Manning describe a method for treating a

respiratory disease in a patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; and a pharmaceutically acceptable carrier, as recited in currently amended claim 1. In further contrast to the presently claimed subject matter, Manning requires the simultaneous use of a PDE inhibitor in order to effect treatment. *See* Manning at page 3, paragraph [0035].

Schmid et al. do not remedy the deficiencies of Manning. Schmid et al. describe compositions and methods for the prevention of vasoconstriction and the preservation of a transplanted organ. According to Schmid et al., the compositions comprise two therapeutic agents selected from the group consisting of BH4 and membrane permeable cGMP analogues. *See* Schmid et al. at the Abstract.

However, like Manning, Schmid et al. do not teach or suggest every element of the presently claimed subject matter. Nowhere do Schmid et al. describe a method for treating a respiratory disease in a patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically

acceptable salts of these compounds; and a pharmaceutically acceptable carrier, as recited in currently amended claim 1. In further contrast to the presently claimed subject matter, Manning requires the simultaneous use of membrane-permeable analogues of cGMP in order to effect treatment. *See* Schmid et al. at page 1, section 1.

Applicants respectfully submit that a proper case of *prima facie* obviousness has not been established because, whether taken alone or together, none of the cited references teach or suggest all the limitations of the claims as required by *In re Wilson*. In particular, none of the cited references teach or suggest a method for treating a respiratory disease in a patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; and a pharmaceutically acceptable carrier, as presently claimed.

In view of the foregoing, it is submitted that, whether taken alone or in combination, Manning and Schmid et al. do not render the presently pending claims obvious within the meaning of 35 USC § 103(a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. At pages 4-5, of the Official Action, claims 5, 7 and 11-15 have been rejected under 35 USC § 103(a) as unpatentable over Manning as evidenced by Schmid et al. and further in view of Juturu et al. (US 2004/0097467) or Rabelink et al. (US 6,544,994).

The Examiner asserts that it would have been obvious to combine the methods for the treatment of respiratory diseases and conditions using a selective iNOS inhibitor and a PDE inhibitor as described in Manning with the use of BH4 as described in Schmid et al. and the use of arginine HCl for the treatment of COPD as described in Juturu et al. or Rabelink et al. to arrive at the presently claimed subject matter.

In view of the following, this rejection is respectfully traversed.

A brief outline of relevant authority is set forth above.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because, whether taken alone or in combination, none of the cited references teach or suggest each and every element of the presently pending claims as required by *In re Wilson*.

Claim 5 depends from claim 1, and further recites an additional compound selected from group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate.

Claim 7 depends from claim 6 and also further recites an additional compound selected from group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate.

Independent claim 11 is directed to a method for treating a respiratory disease in a patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds in combination with a therapeutically effective amount of a further compound selected from the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate; and a pharmaceutically acceptable carrier. Claims 12 and 13 depend from claim 11.

Independent claim 14 is directed to a method for treating muscular dysfunction in a COPD patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds, in combination with a therapeutically effective amount of a further compound selected from the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate, and a pharmaceutically

acceptable carrier.

Independent claim 15 is directed to a method for treating COPD in a patient consisting of the step of administering a pharmaceutical composition comprising a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds in combination with a therapeutically effective amount of a further compound selected from the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate; and a pharmaceutically acceptable carrier.

As discussed above, neither Manning nor Schmid et al. teach or suggest a method for treating a respiratory disease in a patient consisting of administering a pharmaceutical composition comprising a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; and a pharmaceutically acceptable carrier, as presently claimed.

Juturu et al. do not remedy the deficiencies of Manning and Schmid et al. Juturu et

al. describe a method for treating diseases or disorders comprising the administration of an arginine silicate inositol complex. *See* Juturu et al. at the Abstract.

However, like Manning and Schmid et al., Juturu et al. do not teach or suggest every element of the presently claimed subject matter. Nowhere do Juturu et al. describe a method for treating COPD in a patient consisting of administering a pharmaceutical composition comprising a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; an additional compound selected from group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate; and a pharmaceutically acceptable carrier, as presently claimed.

Rabelink et al. do not remedy the deficiencies of Manning, Schmid et al. and Juturu et al. Rabelink et al. describe the use of folic acid and BH4 for the treatment of cardiovascular or neurological disorders by modulation of nitric oxide synthase (NOS). According to Rabelink et al., the pharmaceutical preparations comprise folic acid or folate derivatives, together with BH4 and pharmaceutically compatible active and adjuvant substances. *See* Rabelink et al. at the Abstract.

However, like Manning, Schmid et al. and Juturu et al., Rabelink et al. do not teach

or suggest every element of the presently claimed subject matter. Nowhere do Rabelink et al. describe a method for treating COPD in a patient consisting of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds; an additional compound selected from group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate; and a pharmaceutically acceptable carrier, as presently claimed.

In view of the foregoing, it is submitted that, whether taken alone or in combination, Manning, Schmid et al., Juturu et al., and Rabelink et al. do not render the presently pending claims obvious within the meaning of 35 USC § 103(a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

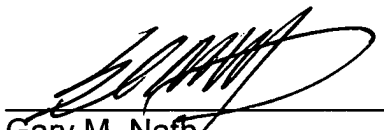
CONCLUSION

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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